Diagnosis and management of adverse drug reactions

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Adverse drug reactions 1 (ADRs)

Definition

• An ADR is ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’.
Adverse drug reactions 2 (ADRs)

Side effect

A side effect is ‘any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug’.

• eg constipation with codeine phosphate
Adverse drug reactions 3 (ADRs)

Adverse event (experience)

• An AE is ‘any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment’.
The monitoring problem

How do we know if a health event is a reaction to a medicine?

- Headache
- Fever
- Vomiting
- Rash
The process of diagnosis 1

Consider all drugs / medicines

• OTC
• contraceptives
• herbal / traditional
• abused drugs / alcohol
• long term treatment

Check
The process of diagnosis 2

• Was the event present before the patient began the medicine?

• Did the event occur within a plausible time period of starting the medicine?
  – headache a few hours after - **Yes**
  – liver failure on the first day - **No**
The process of diagnosis 3

• Allergic type - *previous exposure*
• Foetal abnormality - *stage of pregnancy*
• Consider withdrawal reactions
• Neoplasms - *several years*
• Background frequency
  – agranulocytosis
  – exfoliative dermatitis
The process of diagnosis

Is an event pharmacologically plausible?
• Is it a side effect (class A reaction) of -
  – the drug(s) in question
  – the class?
• Is it a known allergic (class B) reaction
  – the drug(s)
  – the class?
The process of diagnosis 5

- Trial withdrawal
  - is the time to recovery consistent with the action of the drug?
- Rechallenge
  - same pattern?
  - No effect?
The process of diagnosis 6

Investigations

- Blood patterns compared with baseline
- Allergy testing
- Skin biopsy
- Blood levels
The process of diagnosis 7

- Is there the possibility of an interaction?
- Remember
  - OTCs
  - contraceptives
  - herbals / traditional
  - drugs of abuse / alcohol
  - long term medicines
The process of diagnosis

Interaction?

• OK on first drug
• Problems when a second drug is commenced
• Is it the 2nd drug or is it an interaction?
  – had the 2nd drug before?
  – OK when 1st drug withdrawn?
  – knowledge of metabolism
The process of diagnosis 9

Interactions and hepatic metabolism

• Cytochrome P450 enzyme system
  – eg CYP2D6 or CYP2C19
  – inhibition - *increased blood levels*
  – induction - *decreased blood levels*
    (therapeutic effect decreased)
The process of diagnosis 10

Interactions and hepatic metabolism

• Mefloquine metabolised by CYP3A4
  – artemesinin, diazepam, diltiazem, erythromycin, fluoxetine, nifedipine, quinine

• Artemesinin - CYP2B6 & CYP3A4
The process of diagnosis 10

Which drug?

- Timing of drug and reaction
- Difficult when more than one drug is introduced at the same time
- Pharmacology
- Withdrawal
- Rechallenge
Management of ADRs 1

Decisions are made by considering

- Seriousness / severity of ADR
- Seriousness of disease
- Benefit / harm assessment
Management of ADRs 2

If the reaction is serious

• Withdraw suspected (all?) drugs
• Treat urgently
Management of ADRs 3

If the disease is serious

• Consider the effect of not having treatment
• Continue treatment and treat symptoms of reaction if necessary
• Consider an alternative drug
• Stop unnecessary drugs
Management of ADRs 4

If the reaction is mild

- Continue treatment if necessary
- Stop unnecessary drugs
- Consider dose reduction
- Reassure and do nothing
- Symptomatic treatment if warranted
Management of ADRs 5